REMARKS

Claim 55 has been deleted without prejudice. Claims 3, 8, 10, 11, 39 and 50 have been amended to more clearly define Applicants' invention. Support for the amendment can be found, for example, at page 3, lines 29-30 to page 4, lines 1-5, page 4, lines 16-17, page 8, lines 4-11. No new matter has been added. Claims 3, 4, 6, 8 to 12, 14, and 30 to 54 are pending. Claim 3, 8, 39, 49 to 52 and 54 are independent.

Applicants thank the Examiner for indicating withdrawal of objections to claims 10 and 11 and new claim 53 and withdrawal of the 35 U.S.C. § 102(e) rejection to claims 10 and 11 over U.S. Patent No. 6,241,969 to Saidi in the Advisory Action.

Applicants thank the Examiner for conducting a telephonic conference discussing the above-mentioned application, the Office Action and Advisory Action with Applicants' representatives on January 3, 2003 ("Conference"). The features of the invention as claimed and described in the specification were discussed along with the pending rejection.

Objections

Claims 10, 11, 53 and 55

The Examiner has objected to claims 10, 11, 53 and 55 "as not being proper dependent claims." See pages 2 and 3 of the Office Action.

Claim 8 has been amended to delete "dry." Claims 10, 11 and 53 depend from claim 8. Claim 55 has been cancelled without prejudice. Applicants believe that claims 10, 11 and 53 are within scope of amended independent claim 8. In the Advisory Action, the Examiner has indicated that the objections to claims 10, 11 and 53 will be withdrawn. See page 2 of the Advisory Action. Applicants respectfully request reconsideration and withdrawal of this objection.

Rejection under 35 U.S.C. § 102(b)

Claims 10 and 11 have been rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 3,962,430 to O'Neill *et al.* ("O'Neill"). Claims 10 and 11 depend from amended independent claim 8.

In making the rejection, the Examiner contends "the claims contemplate (or explicitly require, as in claim 53) a suspension, and the examiner maintains that when a sterile solution/suspension of a glucocorticosteroid is prepared and sterilized, it is indistinguishable from one prepared from a sterile, dry solid." See page 4 to 5 of the Office Action.[1]

Applicants have discovered a sterile pharmaceutical suspension including an aqueous suspension of a pharmaceutically acceptable inhalation powder is in the form of finely divided particles of mass median diameter (MMD) of less than 10 μm. The particles are heat sterilized and include a glucocorticosteroid or ester, acetal, or salt thereof. See amended independent claim 8.

O'Neill does not disclose an inhalation powder in the form of finely divided particles, the particles being heat sterilized. See independent claim 8. Rather, O'Neill discloses a sterile aqueous suspension for parenteral administration. An aqueous suspension for parenteral administration is not a heat sterilized inhalation powder. O'Neill does not disclose an inhalation powder in the form of finely divided particles, the particles being heat sterilized.

For at least these reasons, claims 10 and 11, which depend from independent claim 8, are not anticipated by O'Neill. Applicants respectfully request reconsideration and withdrawal of this rejection.

Independent claim 3 and claims that depend therefrom

In the Advisory Action, the Examiner indicates that amending claim 3 as indicated in the Amendment filed on December 4, 2002 could result in rejection of claim 3 as being anticipated

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[1] Examiner refers to claim 53. However, the Examiner has not included claim 53 in the § 102 (b) rejection. The amendment of claim 8 address this issue regarding claim 53

by U.S. Patent No. 3,962,430 to O'Neill *et al.* ("O'Neill"). Applicants believe that amended claim 3 as presented in the instant amendment is patentable over O'Neill.

Rejection under 35 U.S.C. § 102(e)

Claims 10 and 11 have been rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,241,69 to Saidi *et al.* ("Saidi"). Claims 10 and 11 depend from independent claim 8.

In making the rejection, the Examiner contends that "the claims contemplate formulation, including solutions, in which the particles are not dry. The examiner maintains that when a sterile solution of a glucocorticosteroid is prepared and sterilized, it is indistinguishable from one prepared from a sterile, dry solid." See pages 4 to 5 of the Office Action.

Saidi does not disclose a sterile suspension including an inhalation powder. The Examiner acknowledges that Saidi discloses sterile solutions of (gluco)corticosteroids. See page 5 of Office Action dated March 12, 2002. The sterile solution of glucocorticosteroids as taught by Saidi is not a suspension including an inhalation powder. Instead, in Saidi the "corticosteroid compounds are present in a dissolved state in the compositions." See abstract of Saidi. The Webster's Ninth New Collegiate Dictionary, 1988 Edition, defines a solution as "act or the process by which a solid, liquid, or gaseous substance is homogeneously mixed with a liquid or sometimes a gas or solid." The Dictionary defines a suspension as "the state of a substance when its particles are mixed with but undissolved in a fluid or solid." Saidi does not disclose a suspension including an inhalation powder.

In the Advisory Action, the Examiner has indicated that the rejection will be withdrawn based on the amendment. See page 2 of the Advisory Action. For at least these reasons, claims 10 and 11 that depend from independent claim 8 are not anticipated by Saidi. Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejections under 35 U.S.C. § 103(a)

Jakupovic combined with Bussey

Claims 3, 4, 6, 8-10, 12, 14, 34-36, 39, 41, 42, 45-48 and 49-55 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 96/32095 to Jakupovic *et al.* ("Jakupovic") combined with Bussey *et al.* ("Bussey"). See page 6 to 8 of the Office Action.

Claims 4, 6, 9-12, 14, 30-31, 34-36, 41, 42, 45-48 and 53 depend from independent claims 3, 8, 39, 49 to 52 and 54.

The Examiner contends "JAKUPOVIC teaches respirable dry particles. See paragraph bridging pages 3 and 4, and the paragraph immediately thereafter. JAKUPOVIC is merely silent regarding sterilization. Bussey teaches sterilization." See pages 5 to 6 of the Office Action.

The Examiner further contends that:

> Bussey teaches sterilization of corticosteroids. It is not clear what Applicant's point is in this statement: (1) This method is inappropriate for sterilization of 'glucocorticosteroids' because it is concerned with 'corticosteroids'; or (2) This method is inappropriate for sterilization of dry particles because it is directed toward 'bulk sterilization.' Regarding (1), according to the definition submitted by Applicant, 'glucocorticosteroids' are a sub-set of 'corticosteroids.' Furthermore, one of the species (prednisolone) taught by BUSSEY is one contemplated by Applicant. See specification at page 4, line 20. Regarding (2), it is not clear how 'bulk sterilization' precludes sterilization of dry particles in bulk. (See page 6 of the Office action)

Regarding claim 39, the Examiner contends that

> Claim 39 recites a product-by-process. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. There does not appear to be any difference between a dry glucocorticosteroid sterilized by heating, as recited in the claims, and a dry glucocorticosteroid sterilized by irradiation or treatment by ethylene oxide. The rejection was made in the previous Office action but not addressed by Applicant in the response. (See page 7 of the Office Action)

In the Advisory Action, the Examiner states "[t]he other rejections would be maintained for reasons of record. Jakupovic clearly contemplates respirable powders and suspensions. The examiner reiterates that the claims are recited in product-by-process form. Applicant has not yet

cited any way that these heat-sterilized products differ from those sterilized by other known methods." See page 2 of the Advisory Action.

Independent claim 8 and claims that depend thereform

As acknowledged by the Examiner, Jakupovic is silent regarding sterilization. Jakupovic does not teach or suggest heat sterilizing an inhalation powder which includes a glucocorticosteroid or ester, acetal, or salt thereof. Indeed, Jakupovic merely teaches a inhalation compound dissolved in a solvent. See abstract of Jakupovic. Nothing in Jakupovic suggests or provides motivation to produce an inhalation powder is in the form of finely divided particles, the particles being heat sterilized.

Bussey does not teach or suggest an inhalation powder is in the form of finely divided particles, the particles being heat sterilized. Bussey merely teaches sterilization by ^{60}Co irradiation. Indeed, Applicants compared heat sterilization with a comparitive example using irradiation. See example 8 in the specification. The results showed that

> budesonide content decreases in samples exposed to β- and γ-irradiation. Several new degradation products were observed, especially for the γ-irradiated sample. In addition the mass balance for both β- and γ-irradiated samples is poor. (See page 19, lines 6 to 10 of the specification.)

As discussed in the Conference, heat sterilization gave superior unexpected results to irradiation sterilization with less degradation of the glucocorticosteroid. See page 19, lines 6 to 13 and Tables 1 and 8 of the specification. One of ordinary skill in the art would not be motivated by the teachings of Jakupovic and Bussey to heat sterilize an inhalation powder. It is well established that "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990).

Independent claim 3 and claims that depend therefrom

Applicants have discovered a pharmaceutically acceptable inhalation powder is in the form of dry finely divided particles of mass median diameter (MMD) of less than 10 μm. The

particles are heat sterilized and include a glucocorticosteroid or ester, acetal, or salt thereof. See amended independent claim 3.

As discussed above, Jakopovic combined with Bussey does not teach or suggest an inhalation powder is in the form of finely divided particles, the particles being heat sterilized. Therefore, it if follows that Jakopovic combined with Bussey does not teach or suggest an inhalation powder is in the form of *dry* finely divided particles, the particles being heat sterilized. As acknowledged by the Examiner, Jakupovic is silent regarding sterilization. Nothing in Jakupovic suggests or provides motivation to produce an inhalation powder is in the form of dry finely divided particles, the particles being heat sterilized. Bussey does not teach or suggest an inhalation powder is in the form of dry finely divided particles, the particles being heat sterilized. As discussed above, Bussey merely teaches sterilization by ^{60}Co irradiation. Indeed, a *prima facie* case alleging that these references teach the features of independent claim 3 has not been presented.

Independent claim 39 and claims that depend therefrom

Applicants have also discovered a pharmaceutically acceptable inhalation powder in the form of finely divided particles having a mass median diameter (MMD) of less than 10 μm, the particles being sterilized by heat treatment at a temperature of from 100°C to 130°C and comprising a glucocorticosteroid or ester, acetal, or salt thereof, wherein the glucocorticosteroid or ester, acetal, or salt thereof, includes an asymmetric acetal structure. See independent claim 39.

As discussed above, Jakupovic combined with Bussey does not teach or suggest an inhalation powder in the form of finely divided particles, the particles being sterilized by heat treatment. Furthermore, Jakupovic combined with Bussey does not teach heat sterilization at a temperature from 100°C to 130°C. See independent claim 39. As discussed above, there is no motivation in the teachings of Jakupovic combined with Bussey to motivate one of ordinary skill in the art to heat sterilize an inhalation powder including a glucocorticosteroid.

Independent claims 49, 50, 51, and 54 and claims that depend therefrom

Applicants have also discovered pharmaceutically acceptable powder, formulation and suspension in the form of heat sterilized, finely divided particles including budesonide, rofleponide or rofleponide palmitate, or ester, acetal, or salt thereof. See independent claims 49, 50, 51 and 54. As discussed above, Jakupovic combined with Bussey does not teach or suggest or provide the motivation for an inhalation powder in the form of finely divided particles, the particles being sterilized by heat treatment. Indeed, Bussey describes the ^{60}Co irradiation of hydrocortisone acetate, isoflupredone acetate, methylprednisolone acetate and prednisolone hydrous. See Table III on page 54 of Bussey. Neither Jakupovic or Bussey teach or suggest a pharmaceutically acceptable powder, formulation and suspension in the form of heat sterilized finely divided particles including budesonide, rofleponide or rofleponide palmitate. Neither does Jakupovic nor Bussey, nor their combination provide any motivation to heat sterilize finely divided particles including budesonide, rofleponide or rofleponide palmitate.

Claim 52 and claims that depend therefrom

Applicants have also discovered a sterile pharmaceutical powder in the form of heat sterilized, dry, finely divided particles including a glucocorticosteroid or ester, acetal, or salt thereof. See independent claim 52. As discussed above, Jakupovic combined with Bussey does not teach or suggest or provide the motivation for an inhalation powder in the form of heat sterilized finely divided particles.

Applicants submit that a hindsight reconstruction is improper. Based on the teachings of Jakupovic in view of Bussey, one of ordinary skill in the art would not at the time the claimed invention was made, have the motivation to combine Jakupovic with Bussey. Thus, without the benefit of Applicants' invention, one of ordinary skill would not arrive at an inhalation powder is in the form of finely divided particles, the particles being heat sterilized.

For at least these reasons, independent claims 3, 8, 39, 49, 50, 51, 52 and 54 and claims that depend therefrom are patentable over Jakupovic combined with Bussey. Applicants respectfully request reconsideration and withdrawal of this rejection.

Jakupovic combined with Bussey further combined with Radhakrishnan and Sequiera

In the Office Action, the Examiner has rejected:

(I) Claims 3, 4, 6, 8-10, 12, 14, 34-36, 39, 41, 42, 45-48 and 49-55 under 35 U.S.C. § 103(a) as being unpatentable over Jakupovic combined with Bussey and U. S. Patent No. 5,192,528 to Radhakrishan ("Radhakrishnan") (see page 7 of the Office Action) and

(II) Claims 3, 4, 6, 8-12, 14, 30, 31, 34-36, 38, 39, 41-48 and 49-55 under 35 U.S.C. § 103(a) as being unpatentable over Jakupovic combined with Bussey and U.S. Patent to Sequiera ("Sequiera") (see page 7 of the Office Action).

In the Advisory Action, the Examiner states "[t]he other rejections would be maintained for reasons of record." See page 2 of Advisory Action.

Claims 4, 6, 9-12, 14, 30, 31, 34-36, 38, 39, 41-48, and 53 depend from independent claims 3, 8, 39, 49 to 52 and 54.

As discussed above, neither Jakupovic nor Bussey teach or suggest an inhalation powder is in the form of finely divided particles, the particles being heat sterilized. See independent claim 8. Neither does Jakopovic nor Bussey teach or suggest an inhalation powder is in the form of dry finely divided particles, the particles being heat sterilized. See independent claim 3.

Neither Radhakrishnan nor Sequeira cure the deficiencies of Jakupovic or Bussey. Specifically, Radhakrishnan discloses an aqueous liposome suspension. See abstract of Radhakrishnan. Sequiera teaches "treating of corticosteroid-responsive diseases of the upper and lower airway passages and lungs, such as asthma, by orally or intranasally administering to said passages and lungs an amount of mometasone furoate." See col. 1, lines 19-23 of Sequeira.

Radhakrishnan or Sequeira do not teach or suggest an inhalation powder is in the form of finely divided particles, the particles being heat sterilized. Thus, the deficiency of Jakupovic combined with Bussey is not cured by either Radhakrishnan or Sequeira. Indeed, a *prima facie* case alleging that these references teach the independent features of claims 3, 8, 39 and 49 to 52 has not been presented.

For at least these reasons, independent claims 3, 8, 39 and 49 to 52 and dependent claims 4, 6, 9-12, 14, 30-31, 34-36, 41, 42, 45-48 and 53 therefrom are patentable over Jakupovic

combined with Bussey, Radhakrishnan and Sequiera. Applicants respectfully request reconsideration and withdrawal of this rejection.

Radhakrishnan

Claims 10 and 11 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Radhakrishnan. See pages 10-11 of the Office Action. Claims 10 and 11 depend from independent claim 8.

In making the rejection, the Examiner contends that "Applicant has not addressed how a sterile suspension of the glucocorticosteroid, prepared and subsequently sterilized, can be distinguished from one prepared from a sterile, dry solid." See pages 8 and 9 of the Office Action.

In the Advisory Action, the Examiner states "[t]he other rejections would be maintained for reasons of record." See page 2 of Advisory Action.

As discussed above, Radhakrishnan does not teach or suggest an inhalation powder is in the form of finely divided particles, the particles being heat sterilized. There is no motivation in the teaching of Radhakrishnan to form an inhalation powder including particles and to heat sterilize the particles.

For at least these reasons, dependent claims 10 and 11 that depend from independent claim 8 are patentable over Radhakrishnan. Applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

Applicants ask that all claims be allowed. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: Jan 9, 03

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Version with markings to show changes made

In the claims:

Claim 55 has been deleted without prejudice.

Claims 3, 8, 10, 11, 39 and 50 have been amended as follows:

--3. (Amended) A pharmaceutically acceptable **inhalation** powder in the form of dry, finely divided particles having a mass median diameter (MMD) of less than 10 μm, said dry particles being **heat** sterilized and comprising a glucocorticosteroid or ester, acetal, or salt thereof, wherein the glucocorticosteroid or ester, acetal, or salt thereof, comprises an asymmetric acetal structure.--

--8. (Amended) A sterile pharmaceutical **[formulation] suspension** comprising **an aqueous suspension of** a pharmaceutically acceptable **inhalation** powder in the form of **[dry,]** finely divided particles, said **[dry]** particles being **heat** sterilized and comprising a glucocorticosteroid or ester, acetal, or salt thereof, wherein the glucocorticosteroid or ester, acetal, or salt thereof, comprises an asymmetric acetal structure, and wherein at least 80% of the particles have a mass median diameter (MMD) of less than 10 μm.--

--10. (Amended) The sterile pharmaceutical **[formulation] suspension** according to claim 8, comprising at least one additive selected from the group consisting of surfactants, pH regulating agents, chelating agents, agents rendering the formulation isotonic and thickening agents.--

--11. (Amended) The sterile pharmaceutical **[formulation] suspension** according to claim 8, wherein the concentration of the glucocorticosteroid or ester, acetal, or salt thereof, ranges from about 0.05 to about 20 mg/ml in the formulation.--

--39. (Amended) A pharmaceutically acceptable **inhalation** powder in the form of **[dry,]** finely divided particles having a mass median diameter (MMD) of less than 10 μm, said **[dry]**

particles being sterilized by heat treatment at a temperature of from 100°C to 130°C and comprising a glucocorticosteroid or ester, acetal, or salt thereof, wherein the glucocorticosteroid or ester, acetal, or salt thereof, comprises an asymmetric acetal structure.--

--50. (Amended) A sterile pharmaceutical formulation comprising a pharmaceutically acceptable powder in the form of heat sterilized**[, dry,]** finely divided particles and comprising budesonide, rofleponide or rofleponide palmitate, or ester, acetal or salt thereof.--